REMARKS

Claims 1, 15, 17, 19, 20, 22, 24, 25, 31, 35, 38, 133-137, 140 and 142-148 are pending in the application prior to entry of amendments submitted herewith, and all of these pending claims are rejected in the Office Action dated January 5, 2007 (the "Office Action"), which Office Action was made final. By amendment herewith, Claims 1, 24, 25, 137 and 142 are being changed, Claims 22 and 144 are being cancelled and new Claims 149-152 are being added. After entry of the amendments submitted herewith, Claims 1, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140 and 142, 143 and 145-152 are pending in the application. None of the amendments introduce new matter, and all of the amendments are made without prejudice to or disclaimer or dedication of any subject matter, and a right is specifically reserved to file continuation and/or divisional applications claiming any subject matter disclosed in the application. Each of the issues raised in the Office Action is addressed below.

I. Correction of Claim Listing

It is respectfully noted that the listing of pending claims on the Summary page of the Office Action omits Claim 140, which in not correct, because that claim has not been cancelled. Claim 140 has been specifically included in specific claim rejections made in the Office Action, indicating that the listing of pending claims on the office action Summary page appears to be an inadvertance. Correction of the pending claim listing to include Claim 140 is requested with the next action issued on this application by the USPTO.

II. Request For Reconsideration and Further Consideration Of The Troha Declaration.

The Examiner stated that the Declaration of Janice M. Troha under 37 C.F.R. §1.132 (the "Troha Declaration") is insufficient to overcome a rejection of claims based on obviousness. The Examiner is requested to reconsider and further consider the Troha Declaration in relation to the

evidence presented of unexpected pharmaceutical properties of the claimed composition for efficacy to treat oral mucositis as a side effect of cancer therapy.

The Examiner apparently gave no or minimal weight to the Troha Declaration, based on asserted reasoning that the Troha Declaration "shows methods of using the compositions," while the "claims are directed to a composition, however not a method of use." The Examiner further stated that "intended use of a composition carries no weight in determining patentability because the compositions suggested by the references are substantially the same as the compositions of the instant claims." The Examiner provided no citations to sections of the MPEP or to any case law in support of these assertions on the legal standard to be applied in assessing the evidence of the Troha Declaration. In fact, the law is contrary to the Examiner's assertions, and a proper consideration of the evidence of unexpected pharmacological properties presented in of the Troha Declaration is requested.

Proper consideration of the Troha Declaration would give weight to evidence that is presented in the Troha Declaration that the claimed composition has unexpected properties, namely, pharmaceutical properties of the composition as being effective to treat for oral mucositis as a side effect of cancer therapy. The Examiner is not being asked to consider the use of the claimed composition, but rather pharmacological properties of the composition, which happen to be important properties for a certain use of the composition, namely, treatment for oral mucositis as a side effect of cancer therapy. But it is the case with every composition invention that the invention is of interest because the properties of the composition make it useful for some purpose, and the examiner must consider and give weight to all evidence of unexpected properties, including unexpected properties relating to pharmacological efficacy for treatment of a particular condition.

In assessing the Troha Declaration, it is important not to confuse the standard applicable for an examiner to make a *prima facie* case of obviousness with the quite different standard for consideration of evidence of unexpected properties presented to rebut a *prima facie* case of obviousness. The case of *In re Dillon*, 919 F2.d 688, 16 USPQ 2d 1897 (Fed. Cir. 1990), is illuminating in that regard.

In *Dillon*, the Court of Appeals for the Federal Circuit sitting *in banc* considered the requirements for stating a *prima facie* case of obviousness based on structural similarity between a prior art composition and the composition of an invention, and found that identification of structural similarity alone may be sufficient, and that it is not necessary to find both structural similarity and some suggestion or expectation in the prior art that the composition of the invention would have the same or similar utility as that of the invention. In that regard, the court in *Dillon* stated:

> Each situation must be considered on its own facts, but it is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from *the prior art* that the claimed compound or composition will have the same or a similar utility *as one newly discovered by applicant*. [*Dillon*, at 919 F.2d 693, emphasis by the court.]

However, a *prima facie* showing of obviousness raises only a presumption of obviousness that can be overcome by rebuttal evidence that may be submitted by an applicant. The court in *Dillon* expressly recognized that after a *prima facie* showing of obviousness has been made based on a structural similarity, that the applicant can rebut such a *prima facie* case of obviousness by showing in effect that what may appear to be obvious due to the structural similarity is in fact not so due the possession of unexpected properties by the invention. In that regard, the court in *Dillon* stated:

> This court, in reconsidering this case *in banc*, reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and that the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case. Such rebuttal or argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly

> improved properties or properties that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument or presentation of evidence that is pertinent. [*Dillon*, at 191 F.2d 693, citations omitted.]

The court in *Dillon* cited to and specifically affirmed the holding in the seminal case of *In re Papesch*, 50 C.C.P.A. 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963), concerning the procedure for rebutting a *prima facie* case of obviousness and the use of evidence of unexpected properties as rebuttal to overcome a *prima facie* case of obviousness. Regarding the procedure of rebuttal following a *prima facie* showing of obviousness, the court in *Dillon* stated:

> The burden then shifts to the applicant, who then can present arguments and/or data to show that what appears to be obvious, is not in fact that, when the invention is looked at as a whole. [*Dillon*, at 919.F2d 696, citation omitted.]

In affirming the holding in *Papesch* concerning rebuttal evidence of unexpected properties of a composition, the court in *Dillon* stated:

> The dissent cites the seminal case of *Papesch*, suggesting that it rejected the principle that we now "adopt," thereby implying that we are weakening *Papesch*. We are doing nothing of the sort. *Papesch* indeed stated that a compound and all of its properties are inseparable and must be considered in the determination of obviousness. We heartily agree and intend not to retreat from *Papesch* one inch. *Papesch*, however, did not deal with the requirements for establishing a *prima facie* case, but whether the examiner had to consider the properties of an invention at all, when there was a presumption of obviousness. [*Dillon*, at 919 F.2d 697, emphasis added, citation omitted.]

In *Papesch*, the Court of Customs and Patent Appeals confronted a situation where the invention was to a new compound that was structurally similar to a prior art compound, but the

compound of the invention possessed potent anti-inflammatory activity in contrast to a structurally related prior art compound. In *Papesh*, the Court rejected reasoning very similar to that proposed by the Examiner here for discounting the evidentiary value of the Troha Declaration, and held that evidence of an unexpected biological or pharmaceutical property can overcome an obviousness rejection based on structural similarity.

In the facts of *Papesch*, the examiner rejected claims to the new compound as being obvious over a prior art reference disclosing a closely related, structurally similar homolog. In responding the rejection, the applicant submitted an affidavit showing that the new compound had the potent anti-inflammatory activity. In maintaining the rejection, the examiner made the following statements, quoted in *Papesch*:

> The affidavit is interesting but irrelevant to the rejection since it is not directed to the subject matter "sought to be patented", namely, the use in the arts of the compounds. The obvious compound is not made less obvious by its properties in an art use. [*Papesch*, at 315 F2d. 383-384, quoting the examiner.]

> The homologous compound being obvious it is not seen how it can become less obvious, as a compound, merely by discovering that in addition to the community of common physical and chemical properties expected of members of an homologues [sic] series it also has other improved or valuable properties. Such discovery is not proper support for a patent for the compound per se. [*Papesch*, at 315 F.2d 385, quoting the examiner, citation omitted.]

The applicant appealed the rejection, which rejection was affirmed by the appeals board. The court in *Papesch*, considering the board's record in affirmation of the rejection, found that the board had not given weight to the affidavit evidence of unexpected anti-inflammatory activity, because the property was a pharmacological property. The court in *Papesch* summarized the board's reasoning as follows:

> In view of that statement [by the board], and since the board found the compounds to be obvious "without shadow of doubt," we are bound to conclude that the board's process of reasoning was first to look at the compounds as chemists to see if they were obvious and, having no doubt that they were, it found no reason to consider the "pharmacological: [sic] facts shown by the affidavit, the existence of which facts has never been questioned. This conforms with the solicitor's oral argument which asked us to ignore the pharmacological properties on the ground that the claimed compounds were "so obvious." [*Papesch*, at 315 F.2d 386.]

The court in *Papesch* then reviewed the case law involving evidence of unexpected properties to overcome a finding of obviousness, and in overturning the board and the examiner's rejection of the claim the court stated:

> From the foregoing cases it will be seen that this and other courts, both before and after the enactment of section 103, have determined the unobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties. Nine of the ten cases above considered, directly and indirectly, involved such properties. Patentability has not been determined on the basis of the obviousness of structure alone. In fact, where patentability was found in the above cases it was found in spite of close similarity of chemical structure, often much closer similarity than we have here.
>
> Returning now to the decision of the board in this case, we think that it rests on one fundamental error of law, namely, the failure to take into consideration the biological or pharmaceutical property of the compounds as anti-inflammatory agents on the ground that to chemists the structure of the compounds would be so obvious as to be beyond doubt, and that a showing of such properties is to be used only to resolve doubt.
>
> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. [*Papesch*, at 315 F.2d 391, emphasis added.]

In the instant application, although it is not admitted that the Examiner has satisfied the requirements for making a *prima facie* showing of obviousness, to the extent that an obviousness rejection made by the Examiner of the claimed composition does satisfy requirements for a *prima facie* showing of obviousness, it is clear from *Dillon* and *Papesch* that the Examiner still must consider and give weight to all evidence of unexpected properties of the claimed composition, including evidence presented in the Troha Declaration of the claimed composition's unexpected property of efficacy to treat for oral mucositis as a side effect of cancer therapy.

III. General Summary of The Subject Matter of the Pending Claims.

Claim 1, the only independent claim pending in the application, is directed to a composition, which has been identified as being useful for the treatment of oral mucositis as a side effect of cancer therapy treatment. As amended herewith, Claim 1 requires that the composition comprise N-acetylcysteine ("NAC"), 5 to 20 weight percent poloxamer 407, and a carrier liquid comprising water. The claims further require that the water and the poloxamer 407 interact to impart reverse-thermal viscosity behavior to the composition and that the composition exhibits reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C, and that when the composition is at some temperature in a range of from 2°C and 8°C that the composition is in the form of an aqueous solution with poloxamer 407 and the NAC dissolved in the water. All of the pending dependent claims depend directly or indirectly from Claim 1, and each dependent claim therefore includes all of the features recited in Claim 1, as well as the additional features recited in dependent claim and any intervening claim(s). The claimed composition has been found to have a pharmaceutical property of being effective for treating oral mucositis as a side effect of cancer therapy.

IV. Rejection Under 35 U.S.C. §103(a) Based on Krezanoski et al. in view of Boggs et al.

The Examiner rejected Claims 15, 22-23 and 136-141 under 35 U.S.C. §103(a) based on an assertion of unpatentability over Krezanoski (U.S. Patent 5,188,373) in view of Boggs et al. (U.S. Patent 5,358,705). The rejection is traversed.

In rejecting claims based on a combination of Krezanoski and Boggs et al., the Examiner stated that the test is what the combination of the references would have suggested to those of ordinary skill in the art. However, even if Krezanoski and Boggs et al. in combination make a *prima facie* showing of obviousness, still the evidence of unexpected pharmaceutical property of the claimed composition as presented in the Troha Declaration must be considered as rebuttal to such a *prima facie* case, to show that the claimed composition is in fact not obvious.

However, it is respectfully submitted that (1) one of ordinary skill in the art would not consider Krezanoski and Boggs et al. in combination because of their apparently disparate subject matters; (2) even if Krezanoski and Boggs et al. were to be considered in combination, one of ordinary skill in the art would not use the drug delivery vehicle of Krezanoski for delivery of the drug disclosed by Boggs et al.; and (3) in any event, evidence of unexpected pharmaceutical properties of the claimed composition adequately rebut a case of obviousness based on a combination of the references.

It is respectfully submitted that one of ordinary skill in the medical art, such as a doctor, pharmacist or other medical professional, would not consider Krezanoski and Boggs et al. in combination, because of their disparate, nonanalogous subject matters. Both references concern drug delivery, but they are so different in their drug delivery objectives that one of ordinary skill in the art would not consider them in combination. In that regard, Krezanoski is focused on drug delivery to a mucous membrane generally, while Boggs et al. are focused on delivery of a specific drug to the surface of the teeth for a surface treatment of those teeth. Krezanoski addresses problems with delivering a drug to the mucous membrane and discloses that the drug delivery vehicle composition of Krezanoski has been found to increase absorption of the drug by the mucous membrane. In contrast, Boggs et al. address problems with plaque and periodontal disease through surface treatment of the teeth to create a barrier on the surface of the teeth to impede bacterial access to the tooth surface. The drug delivery mechanisms of Boggs et al. and Krezanoski et al. are simply so different that one of ordinary skill in the art would not consider

them together, especially because delivery of an active pharmaceutical to the surface of teeth as disclosed by Boggs et al. would be detrimental to achieving the mucous membrane delivery sought by Krezanoski, and vice verse. On their faces, these references are not compatible. The enclosed Declaration of Gary J. Rosenthal (the "Rosenthal Declaration") is referred to as further evidence that the drug delivery mechanisms are so different, and it would be so obvious to a medical practitioner that the approach of one reference would be detrimental to the objective of the other reference, that the references are not combinable.

However, even if the references were to be considered in combination, one of ordinary skill in the art would not combine the drug disclosed by Boggs et al. (a metal ion complex with an N-acetylated amino acid, such as NAC) with the drug delivery vehicle disclosed by Krezanoski (which is disclosed to increase absorption of drug by the mucous membrane), as proposed by the Examiner. The only purpose disclosed by these references for use of NAC is in Boggs et al. as a weak complexing agent for delivery of the metal ion to the surface of the teeth for binding of the metal ion at the tooth surface, and one of ordinary skill in the art would recognize that the increased absorption of the metal ion by the mucous membrane according to Krezanoski would be unsuitable for treatment of the tooth surface according to Boggs et al. because of at least the following: (1) increased absorption by the mucous membrane would result in a loss of drug available for the intended surface treatment of the teeth and an increase in the potential for side effects to untargeted bystander cells, and with no apparent benefit associated with the loss of drug or the increased potential for side effects to bystander cells, and (2) the metal ions used by Boggs et al. are known to present significant toxicitiy risks to humans. Reference is made to the Rosenthal Declaration as evidence of what the combined teachings of Krezanoski and Boggs et al. would and would not suggest to one of ordinary skill in the art, and that one of ordinary skill in the art would not find obvious the claimed composition.

Also, even if the issue of obviousness based on Krezanoski and Boggs et al. were close, and it is not, the unexpected pharmaceutical properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy is sufficient to rebut a *prima facie* case of obviousness based on Krezanoski and Boggs et al. In that regard, reference is made to the Troha Declaration. Reference is also made to the Rosenthal Declaration, and particularly

section III of the Rosenthal Declaration, including the statement on page 18 that nothing in Krezanoski or Boggs et al. suggests that the claimed composition would possess properties beneficial for effective treatment of oral mucositis as a side effect of cancer therapy, and that such properties would be unexpected from the disclosures of Krezanoski and Boggs et al.

It is respectfully submitted that the rejection under 35 U.S.C. § 103(a) based on Krezanoski et al. in view of Boggs et al. should be withdrawn.

V. Rejection Under 35 U.S.C. § 103(a) based on Boggs et al. in view of Stratton et al.

The Examiner rejected Claims 1, 15, 20, 22, 24-25, 35, 38, 137, 140 and 142-148 under 35 U.S.C. §103(a) based on an assertion of unpatentability over Boggs et al. in view of Stratton et al. (U.S. Patent 5,358,705). The rejection is traversed.

In many ways, consideration of Boggs et al. and Stratton et al. is similar to the consideration of Krezanoski and Boggs et al. discussed above, because Krezanoski and Stratton et al. are using similar poloxamer formulations, but for different drug delivery objectives, and the teachings of Krezanoski concerning increased absorption of drugs by mucous membranes when using such poloxamer formulations is equally as relevant to a discussion of Boggs et al. and Stratton et al.

The Examiner noted in the Office Action that Boggs et al. disclose that oral care compositions used for surface treatment of the teeth may contain, in addition to the active material of a metal ion complex with N-acetylated amino acid, from 0% to about 10% surfactant, and that poloxamers are identified as one potential for use as a surfactant. The Examiner's reference specifically to Pluronic F-127 must be to Example I presented by Boggs et al., because that is apparently the only place where Boggs et al. mention Pluronic F-127.

In making the rejection based on an asserted combination of Boggs et al., it appears as though the Examiner's factual basis for a finding of obviousness is as follows:

1. Boggs et al. disclose the main components of the claimed composition in compositional ranges covered by the claims, namely, NAC (as the N-acetylated

amino acid in the metal ion complex, which complex is disclosed by Boggs et al. at column 4, lines 11-18 to be used in the composition of Boggs et al. in an amount of 0.05 to 10%) and poloxamer 407 (as a surfactant, which as disclosed by Boggs et al. at column 6, lines 1-18 may be present in an amount of 0 to 10%, and may be a poloxamer, and which could be Pluronic F-127 based on the use of that polymer in Example 1 of Boggs et al.);

2. Boggs et al. do not disclose that any of its compositions display reverse-thermal viscosity behavior;

3. But Stratton et al. disclose properties of poloxamer formulations, which do not include gelation at the concentrations of poloxamer listed by Boggs et al. (presumably based on the disclosure in Stratton et al. at column 6, lines 35-45 that a gel will not form when the concentration of "polyoxyethelene[sic]-polyoxypropylene" block copolymer in water or dilute buffer is outside of the range of 20 to 30 percent);

4. And one of ordinary skill in the art would be motivated by a desire to inhibit gel formation but still have an increased viscosity when introduced into the body to prolong the release of the active agent, as disclosed by Stratton et al.

5. Therefore, one of ordinary skill in the art would find obvious the claimed combination of particular concentrations of NAC and poloxamer 407 formulated in a composition with reverse-thermal viscosity behavior.

This apparent chain of reasoning is tenuous at best, and the Examiner offers no support for the asserted motivation that one of ordinary skill in the art would want to inhibit gel formation or prolong release of the active agent in the dental treatment application of Boggs et al. Also, this reasoning ignores the different contexts of drug delivery discussed by each of Boggs et

al. and Stratton et al. and the different problems associated therewith, and without any reasoned or common sense basis for support proposes a purported motivation of one of ordinary skill in the art to modify the composition of Boggs et al. to achieve proffered objectives (inhibiting gel formation while increasing viscosity and prolonging drug release), which motivation is contrary to the fact that the teeth surface treatment of Boggs et al. is not a sustained, or prolonged, drug delivery application and that prolonging drug delivery would be detrimental to a normal desire in the situation of Boggs et al. to make the metal ion active readily available for binding at the tooth surface.

Upon a careful consideration of the teachings of Boggs et al. and Stratton et al., and supplemented by the teachings of Krezanoski and viewed from the perspective of the skill and experience of one of ordinary skill in the medical art, it is clear that the claimed composition is not obvious. Moreover, in any event, the evidence of unexpected pharmaceutical properties as disclosed in the Troha declaration negates a finding of obviousness based on Boggs et al. and Stratton et al.

In considering Boggs et al. and Stratton et al., it is respectfully initially submitted that one of ordinary skill in the art in the medical field would not consider Boggs et al. and Stratton et al. in combination, because of their disparate, nonanalogous subject matters. Both references concern drug delivery, but they are so different in their drug delivery objectives that one of ordinary skill in the art would not consider them in combination. In that regard, Boggs et al. are focused on delivery of a specific drug to the surface of the teeth for a surface treatment of those teeth, while Stratton et al. are focused on sustained systemic delivery of polypeptides, and particularly proteins, through parenteral administration. Accordingly, Stratton et al. address problems associated with parenteral delivery of polypeptides for systemic sustained release applications, while Boggs et al. address problems with plaque and periodontal disease through surface treatment of the teeth to create a barrier on the surface of the teeth to impede bacterial access to the tooth surface for binding of the active at the tooth surface. As was the case with Krezanoski, so also the drug delivery mechanisms of Boggs et al. and Stratton et al. are simply so different that one of ordinary skill in the art would not consider them together, especially because sustained delivery suitable for parenteral administration disclosed by Stratton et al. would be

detrimental to making the metal ion active readily available for binding to surfaces of the teeth, and vice verse. The sustained release mechanisms of Stratton et al. suggested by the Examiner to be beneficial to Boggs et al. would actually be detrimental for the application of Boggs et al., which is based on ready availability of the metal ion active for binding at the tooth surface. (*See*, Boggs et al. at column 3, lines 34-52). The application of Boggs et al. is not a sustained release application and drug delivery features that promote sustained release suitable for the parenteral applications of Stratton et al. would be detrimental to the purposes of Boggs et al. by impeding ready access of the metal ion to the tooth surface for binding there. On their face, these references are not compatible. The enclosed Declaration of Gary J. Rosenthal (the "Rosenthal Declaration") is referred to, however, as further evidence that the drug delivery mechanisms are so different, and it is so obvious that the approach of one would be detrimental to each other, that the references are not combinable as suggested by the Examiner.

However, even if the references were to be considered in combination, one of ordinary skill in the art would not combine the drug disclosed by Boggs et al. (a metal ion complex with an N-acetylated amino acid, such as NAC) with attributes of a sustained delivery drug delivery vehicle as disclosed by Stratton et al., as proposed by the Examiner. As was the case with Krezanoski above, so also here the only purpose disclosed by the references for use of NAC is in Boggs et al. as a weak complexing agent for delivery of a metal ion active to the surface of the teeth for binding of the metal ion at the tooth surface. Therefore, Boggs et al. desire ready access for the metal ion active to the tooth surface for binding there. The sustained release aspect of Stratton et al. from a poloxamer matrix would be recognized by one of ordinary skill in the art as being detrimental for the application of Boggs et al, because such a matrix would delay release of the metal ion active and thereby impede ready access of the metal ion active to the tooth surface for binding. Moreover, Stratton et al. specify that their active material, polypeptide, be present in their drug delivery composition in the form of a precipitate, whereas Boggs et al. teach that the metal ion should be delivered in the form of a weak complex with the N-acetylated amino acid (e.g., NAC) and that insoluble precipitates should be avoided. Reference is also made to the Rosenthal Declaration as evidence of what the combined teachings of Boggs et al. and Stratton et al. would and would not suggest to one of ordinary skill in the art, and that one of ordinary skill

in the art considering Boggs et al. and Stratton et al. would not find obvious the claimed composition.

Moreover, the poloxamer formulations of Stratton et al. are similar to the drug delivery vehicle of Krezanoski, which Krezanoski discloses have been found to increase drug absorption by the mucous membrane. As discussed in the Rosenthal Declaration, a person skilled in the medical art wanting to perform a surface treatment of the teeth using the metal ion complex with NAC as disclosed by Bogs et al., would not use the delivery vehicle of Stratton et al. because of the knowledge in the art, as disclosed by Krezanoski, that formulations of that type increase drug absorption by the mucous membrane. For the same reasons as discussed above with respect to Krezanoski and Boggs et al., one of ordinary skill in the art would recognize that increased absorption of the metal ion by the mucous membrane as disclosed by Krezanoski from poloxamer formulations of the type disclosed by Krezanoski and Stratton et al. would be unsuitable for treatment of the tooth surface according to Boggs et al. because of at least the following: (1) increased absorption by the mucous membrane would represent a loss of drug available for the desired surface treatment of the teeth and an increase in potential for side effects to untargeted bystander cells and with no apparent benefit associated with the loss of drug or the increased potential for side effects to bystander cells, and (2) the metal ions used by Boggs et al. are known to present significant toxicity risks to humans. Reference is again made to the Rosenthal Declaration as evidence in this regard.

Also, even if the issue of obviousness based on Stratton et al. and Boggs et al. were close, which it is not, the unexpected pharmacological properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy is sufficient to rebut any prima facie case of obviousness based on Boggs et al. and Stratton et al. In that regard, reference is made to the Troha Declaration. Reference is also made to the Rosenthal Declaration, and particularly section IV of the Rosenthal Declaration, including the statement on page 21 that nothing in Boggs et al. or Stratton et al. suggest that the claimed composition would possess properties beneficial for effective treatment of oral mucositis as a side effect of cancer therapy, and that such properties would be unexpected from the disclosures of Boggs et al. and Stratton et al.

It is respectfully submitted that the rejection under 35 U.S.C. § 103(a) based on Boggs et al. in view of Stratton et al. should be withdrawn.

VI. Rejection Under 35 U.S.C. § 103(a) based on Dobrozsi et al.

The Examiner rejected Claims 1, 15, 19, 31, 35, 38, 133-137, 142-143 and 146 based on an assertion of unpatentability over Dobrozsi et al. (U.S. Patent 6,503,955) under 35 U.S.C § 103(a). The rejection is traversed.

This obviousness rejection follows rejections in the prior office action based on anticipation by Dobrozsi et al. under 35 U.S.C. § 102(e) and obviousness based on Dobrozsi under 35 U.S.C. § 103(a). The Examiner has withdrawn the rejection based on anticipation, but has again stated a rejection based on obviousness, applied to a different group of claims.

As stated in the response to the prior office action, it is apparent from a reading of Dobrozsi et al. that one of ordinary skill in the art considering Dobrozsi et al. would recognize the following from the teachings of Dobrozsi et al.:

1. An advantageous drug delivery vehicle is a pourable liquid vehicle with the compositional attributes disclosed by Dobrozsi et al., and formulated to convert from a pourable liquid to a gel due to dilution with bodily fluids;
2. A teaching away from the use of drug delivery compositions with reverse-thermal gelling properties based on a combination of poloxamer and water as being inadequate because the gel structure readily dissolves in aqueous environments, an inadequacy addressed by Dobrozsi et al. with their pourable liquid vehicle with gel formation triggered by dilution with bodily fluids rather than based on temperature changes; and
3. NAC is useful in the pourable liquid vehicle of Dobrozsi et al. as an expectorant\mucolytic.

Also as discussed in the response to the prior office action, based on these recognitions of the teachings of Dobrozsi et al., if one of ordinary skill in the art were to attempt to modify the pourable liquid vehicle of Dobrozsi et al., the modification would be guided by the teachings of Dobrozsi et al. concerning the desirability of triggering gelation by dilution with bodily fluids and the inadequacy of reverse-thermal gelation. Any such modification by one of ordinary skill in the art would, therefore, be away from compositions containing reverse-thermal gelling and toward the dilution-triggered gelling of the pourable liquid vehicle of Dobrozsi et al., and it would not, therefore, be obvious for one of ordinary skill in the art to make modifications in the direction of the features of the claimed composition, because one of ordinary skill in the art would have no motivation to modify the composition of Dobrozsi et al. to achieve purposes different from and contrary to the teachings of Dobrozsi et al.

The Examiner makes an assertion on page 4 of the Office Action to the effect that Dobrozsi et al. disclose that its compositions have reverse-thermal viscosity behavior. It is believed that the Examiner must be referring to that section of Dobrozsi et al. at column 4, line 49 through column 5, line 23, where Dobrozsi et al. discuss determination of a "triggered viscosity ratio" involving measurement at 25°C of the viscosity of their pourable liquid vehicle and measurement at 37°C of the viscosity of the gel that is formed by dilution of the pourable liquid vehicle. As discussed in the Declaration of Antony James Mathews (the "Mathews Declaration"), this disclosure by Dobrozsi et al. does not relate to reverse-thermal viscosity behavior. Reverse-thermal viscosity behavior is a property of a composition in response to a change in temperature that does not involve a compositional change, whereas the gelling described by Dobrozsi et al. is caused by a compositional change, and not by a temperature change.

As discussed in the Mathews Declaration, the pourable liquid vehicle of Dobrozsi et al. is formulated to gel in response to compositional change (dilution) rather than in response to increasing temperature (reverse-thermal behavior), and it is clear that the pourable liquid vehicle of Dobrozsi et al. does not inherently have the property of reverse-thermal viscosity behavior of the type recited in the claims, even when the pourable liquid vehicle of Dobrozsi et al. is made using poloxamer 407, the polymer specified in the claims. The Mathews Declaration

summarizes selection and testing for reverse-thermal viscosity behavior of four test compositions that are compositionally within the broad teachings of Dobrozsi et al. These compositions were all made using 26% poloxamer 407, the minimum permitted by Dobrozsi et al. and the closest concentration to the range of 5 to 20% poloxamer 407 recited in the claims. The compositions were also prepared with sufficient water for preparation of aqueous solutions, which is also a requirement of the claims. Of the four test compositions, one could not be mixed to a homogenous state and therefore was not tested for viscosity. Another composition did not satisfy the requirements of Dobrozsi that the viscosity of their pourable liquid vehicle must be less than 7000 cP, and so that test composition could not possibly qualify as a pourable liquid vehicle within the teachings of Dobrozsi et al., even though it is within the broad compositional teachings of Dobrozsi et al. Although not qualifying as a pourable liquid vehicle of Dobrozsi et al. because of its extremely high viscosity, this composition did exhibit reverse-thermal viscosity behavior. The remaining two test compositions had lower viscosities consistent with the viscosity requirements of Dobrozsi et al. for their pourable liquid vehicle, but neither of those compositions exhibited reverse-thermal viscosity behavior.

Clearly, considering the teaching away of Dobrozsi et al. from reverse-thermal gelling poloxamer as being inadequate and considering that the pourable liquid vehicles of Dobrozsi et al. in fact do not inherently include reverse-thermal viscosity behavior, even when made using poloxamer 407, the claimed composition is not obvious over the teachings of Dobrozsi et al. Moreover, the evidence presented in the Troha Declaration of unexpected pharmaceutical properties in the treatment of oral mucositis as a side effect of cancer therapy further negates a finding of obviousness based on Dobrozsi et al.

It is respectfully submitted that the rejection under 35 U.S.C. § 103(a) based on Dobrozsi et al. should be withdrawn.

VII. Rejection Under 35 U.S.C. § 103(a) based on Dobrozsi et al. in view of Stratton et al.

The Examiner rejected Claims 17, 20, 24-25, 137, 140, 144-145 and 147-148 based on an assertion of unpatentability over Dobrozsi et al. in view of Stratton et al. under 35 U.S.C § 103(a). The rejection is traversed.

Dobrozsi et al. and Stratton et al. are each discussed above, and it is clear from the above discussions that the teachings of Dobrozsi et al. and Stratton et al. are not combinable in a manner suggested by the Examiner, because they are fundamentally different. Dobrozsi et al. teach away from reverse-thermal gelling behavior for drug delivery, while in direct opposition Stratton et al. require what Dobrozsi et al. teach away from.

Ignoring the contrary teachings of Dobrozsi et al. and Stratton et al., the Examiner asserts, on page 7 of the Office Action:

> It would also have been obvious to one of ordinary skill in the art to have used the delivery system [of Stratton et al.] comprising 20 to 30 percent poloxamer and the theory to deliver the active agents of the primary reference [Dobrozsi et al.] motivated by the desire to provide a sustained release composition that exist in liquid form and gels when introduced into the body wherein the therapeutic composition is released over a period of time, as disclosed by the secondary reference.

In assessing the Examiner's assertion of what one of ordinary skill in the art would appreciate from the teachings of Dobrozsi et al. and Stratton et al., it is initially noted that the active material disclosed by Dobrozsi et al. (which the Examiner finds obvious to deliver in a sustained release composition of the type disclosed by Stratton et al.) is NAC, which Dobrozsi et al. disclose as only one possible drug in a very long and extensive listing of drugs and only then for use as an expectorant/mucolytic. As discussed in the Troha Declaration, an expectorant or mucolytic is an agent used to break down and expel mucous from the respiratory tract. Use of NAC as an expectorant/mucolytic as disclosed by Dobrozsi et al. would, therefore, logically involve administration of the NAC only to the respiratory tract to contact the mucous to be broken down and expelled by action of the NAC. But the compositions of Stratton et al. are

designed for parenteral placement for sustained delivery of polypeptides in the body after the parenteral placement.

The Examiner's statement of motivation of one of ordinary skill in the art for sustained release of NAC into the body over time makes no sense for an expectorant/mucolytic, which is the only use for which NAC is disclosed by either Dobrozsi et al. or Stratton et al. In fact, there would be no motivation to modify the composition of Stratton et al. for use with NAC as an expectorant/mucolytic as disclosed by Dobrozsi et al., and such a combination makes no sense. Stratton et al. is directed to sustained delivery polypeptides from a composition parenterally placed in a patient. NAC is not a polypeptide, and as an expectorant/mucolytic would not be administered by parenteral placement, such as through implantation or through use of an implantable pump as disclosed by Stratton et al. Moreover, Dobrozsi et al. specifically teach away from the use of reverse-thermal gelling formulations such as those of Stratton et al., which is also a teaching away from using such reverse-thermal gelling compositions for delivery of NAC for the disclosed use as an expectorant/mucolytic. Reference is again made to the Mathews Declaration as evidence concerning the teachings of Dobrozsi et al. and the teaching away by Dobrozsi et al. from the use of reverse-thermal gelling formulations based on poloxamer 407. Reference is also made again to the Rosenthal Declaration as evidence concerning the teachings of Stratton et al., including in relation to sustained delivery of polypeptides through parenteral placement.

Additionally, the Troha Declaration discloses evidence of unexpected pharmaceutical properties of the claimed composition that also negate any finding of obviousness over Dobrozsi et al. and Stratton et al.

It is believed that all of the issues raised in the Office Action have been addressed herein. Should the Examiner maintain any of the rejections of any of the pending claims, it is respectfully requested that it be pointed out with particularity how the cited reference(s) meet each and every term of each claim with respect to which rejection is maintained. In the absence of a persuasive showing to that effect, all pending claims should be allowed.

The application is believed to be in condition for allowance and allowance of all pending claims is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Date: July 5, 2007

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